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Outcome of Chinese Patients With Chronic Myeloid Leukaemia (CML) Underwent Allogeneic Bone-Marrow Transplantation (BMT)

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Clinical studies have shown that patients with chronic myeloid leukaemia (CML) treated with allogeneic bone-marrow transplantation (BMT) experience not only prolonged disease-free survival but also complete cure in some. Therefore, we followed a cohort of 81 Chinese patients who received allogeneic BMT.

Patients and Methods: **The donors were either relatives (65 siblings, 1 parent) or unrelated volunteers (15). BMT was performed at a median interval of 11.6 months from diagnosis of CML, and the stages of disease before BMT were: first chronic phase (60 patients), accelerated or second chronic phase in (10 patients), and blastic crisis (11 patients). Three conditioning regimens were employed: Bu-Cy, Cy-TBI, or Bu-Cy-TBI. Standard cyclosporin and short methotrexate protocol were used for acute graft-versus-host disease (GvHD) prophylaxis.**

Results: **There were five graft failures with three after related BMT. Patients after related or unrelated BMT had a comparable rate of neutrophil recovery (median = 22 days), but significant delay in platelet recovery occurred after unrelated BMT (median = 34 vs. 20 days, $P < 0.05$). The latter also had higher incidence of acute GvHD (73% vs. 41%, $P < 0.05$), although the incidence of chronic GvHD was not different between groups. At a median follow-up of 43.5 months, patients after related BMT had a significantly better rate of disease-free survival (68% vs. 37.3%, $P < 0.05$) and overall survival (81% vs. 38.9%, $P < 0.05$) at 4 years. Subgroup analysis of patients after related BMT showed the outcome was better when they were transplanted at first chronic phase. Multivariate analysis showed that advanced disease (RR = 2.01, 95% CI = 1.48–2.73) significantly worsened the outcome of BMT, whereas the presence of chronic GvHD had a protective effect against relapse and survival (RR = 0.09, 95% CI = 0.02–0.38).**

Conclusion: **Allogeneic BMT is a curative form of treatment for patients with CML. Treatment outcome is best for those who undergo transplants from HLA-matched siblings during the first chronic phase. Am. J. Hematol. 61:85–89, 1999.** © 1999 Wiley-Liss, Inc.

Key words: allogeneic bone-marrow transplantation (BMT); chronic myeloid leukaemia (CML); graft-versus-host disease (GvHD); outcome

INTRODUCTION

Management of patients with chronic myeloid leukaemia (CML) has evolved rapidly over the last decade [1–5]. Allogeneic bone-marrow transplantation (BMT) has become the gold standard in offering treatment to these patients [6–8]. Unfortunately, fully HLA-matched sibling donors are not always available. Therefore, one antigen-mismatched family member or unrelated volunteered donor is increasingly used [9].

Here, we summarise our results of allogeneic BMT for Chinese patients with CML receiving non-T-cell depleted bone-marrow graft at a single institution in Hong Kong. We also look at the prognostic factors that influence the outcome.

PATIENTS AND METHODS

From May 1990 to April 1996, 81 Chinese patients living in Hong Kong with Philadelphia chromosome

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positive CML received allogeneic BMT at Queen Mary Hospital, Hong Kong. Patients were grouped into three categories according to their disease status immediately before BMT. Group I included all patients in their first chronic phase (60) and group II consisted of patients in the accelerated or second chronic phase (10). Patients who remained in blastic phase were in group III (11). Donor and recipients' HLA A and B antigens were matched by serological methods, and their HLA DR antigens were typed serologically in the first 53 cases and by molecular methods in the remaining ones.

Patients received one of the following three conditioning regimens:

1. Busulfan 4 mg/kg from days −7 to −4 and cyclophosphamide 60 mg/kg on days −3 and −2 (Bu-Cy);
2. Cyclophosphamide 60 mg/kg on days −5 and −4 and fractionated total body irradiation 2 Gy twice daily from days −3 to −1 (Cy-TBI);
3. Busulfan 1.75 mg/kg from days −9 to −6, cyclophosphamide 25 mg/kg on days −5 and −4, fractionated total body irradiation 2 Gy twice daily from days −3 to −1 (Bu-Cy-TBI).

Donor bone marrow was harvested on day 0 at 15 ml/kg of recipient body weight. All patients received a median dose of 3.55×10^8 mononuclear cells per kg of recipient body weight. They were nursed in isolated rooms and received appropriate anti-bacterial, anti-fungal, and anti-viral prophylaxis until marrow recovery occurred. Uniform graft-versus-host disease (GvHD) prophylaxis with i.v. cyclosporin of 1.5 mg/kg twice daily and short methotrexate (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11) were given to all patients who received related and unrelated transplantation. Colony-stimulating factors and intravenous immunoglobulin were not routinely given. The severity of acute GvHD was graded according to the standard grading system [10,11].

STATISTICAL ANALYSES

t test or X^2 test was used to compared their baseline clinical data. Statistical significance was taken at $P < 0.05$. An event was defined as relapse or death. Overall survival (OS) and disease-free survival (DFS) were calculated from the time of BMT to the time of last follow-up and to the time when an event occurred, respectively. Relapse rates and survival curves were estimated by the product-limit method of Kaplan and Meier. Univariate comparisons were performed by using log-rank statistics and the Cox proportional hazard model was used for multivariate analyses.

RESULTS

Demographic

Fifty-seven males and 24 females at a median age of 33 years (r = 13–50) were included. Sixty-six received related (65 sibling and 1 parental) donor grafts and 15 unrelated BMT was performed (Table 1). There were six cases with one HLA-antigen mismatch (five related and one unrelated). The median time from diagnosis to BMT was 11.6 months (r = 2.8–124.6). This was significantly shorter in those who received related BMT (8.5 vs. 23.7 months, $P < 0.05$). Male patients were also transplanted significantly earlier than female (10.8 vs. 29.2 months, $P < 0.05$) ones. There was a significantly longer interval from diagnosis to BMT in patients from groups II and III compared with those in group I (8.6 vs. 36.6 vs. 27.6 months, $P < 0.05$).

Engraftment

After BMT, five patients developed primary graft failure that resulted in early mortality. Three of them received related BMT (one with one antigen mismatched) and two unrelated. All failed to respond to haematopoietic growth factors and supportive therapy and died of complicating infections.

Of the remaining 76 patients, their median time to neutrophil count above 0.5×10^9/l was comparable at 20–21 days. However, significantly earlier platelet recovery occurred in patients after related BMT (20 vs. 34 days, $P < 0.05$)

Acute and Chronic GvHD

Seventy-eight patients (including two with primary nonengraftment) were evaluated for incidence of acute GvHD. Clinical GvHD was observed in 37 of them (47.4%). Severe grade III to IV GvHD was found in 7 of the 63 (11.1%) patients after related BMT, and this was significantly less than those after unrelated BMT (7 of 15 (46.7%) $P < 0.05$). Twelve (85.7%) of all 14 patients with grade III to IV GvHD died.

Seventy-one patients survived for more than 100 days after BMT and were eligible for assessment of chronic GvHD. Twenty-eight (46.7%) of the 60 patients who received related BMT and 5 of 11 (45%) patients in the unrelated group had clinical features of chronic GvHD. No significant difference was observed among them.

Follow-up and Survival

At a median follow-up of 43.5 months (r = 1.3–74.1 months), there were 17 deaths (21%). These included graft failure in five (including two with hyperacute

TABLE I. Demographic and Outcome of Patients after Allogeneic BMT*

	All	Related BMT	Unrelated BMT	
Male	57	48	9	
Female	24	18	6	*p* value[a]
Age (year)	33	33.5	32	>0.05
HLA				
identical		61	14	
A mismatched		2	1	
B mismatched		2	0	
DR mismatched		1	0	
Disease status before BMT (N)				
Group I	60	52	8	
Group II	10	7	3	
Group III	11	7	4	
Median time from diagnosis to BMT (months)	11.6	8.5	23.7	<0.05
Group I	8.6	8.1	23.0	>0.05
Group II	36.6[b]	32.4	40.7	>0.05
Group III	27.8[b]	27.6	25.8	>0.05
Male	10.8	8.1	18.8	>0.05
Female	29.2[c]	12.8	33.9	<0.05
Conditioning regimens				
Cy-TBI	26	19	7	
Bu-Cy	37	36	1	
Bu-Cy-TBI	16	10	6	
Other[d]	2	1	1	
Engraftment				
Platelet > 25 × 10^9/l		20 (n = 60) (n = 12)	34	<0.05
Platelet > 50 × 10^9/l		24 (n = 60) (n = 10)	45	<0.05
Neutrophil > 0.5 × 10^9/l		22 (n = 63) (n = 13)	23	>0.05
Acute GvHD				
Grade 0–II	64	56	8	
Grade III–IV	14	7	7 (2)	
Graft failure	3	3	—	
Overall acute GvHD		41%	73%	<0.05
Chronic GvHD				
Presence	38	32	6	
Absence	33	28	5	

*Primary nonengraftment in five patients. They are three related transplants from group III and two unrelated transplants from group I. (2) Denotes that two patients have hyperacute grade IV GvHD without evidence of engraftment. Group I: patients in their first chronic phase; group II: patients with features of accelerated phase; group III: patients transplanted after induction chemotherapy for blastic crisis.

[a]*P* value denotes results obtained by comparison between related and unrelated transplant.

[b]$P < 0.05$ when group II or group III compared with group I in all the studied patients.

[c]$P < 0.05$ when all female patients compared with all male patients.

[d]Etoposide (VP-16) containing regimens.

GvHD), severe GvHD in six, veno-occlusive disease in two, interstitial pneumonitis in three, and respiratory failure as the result of bronchiolitis obliterans in one.

Fourteen patients (13 related and 1 after unrelated BMT) relapsed at a median time of 11.5 months (r = 3.2–44.1 months). Six died eventually because of uncontrolled leukaemia and complications. Actuarial DFS and OS at 4 years were 60.3% and 74.9% after related BMT and 37.3% and 38.9% after unrelated BMT, and these were of statistical significance ($P < 0.05$) (Fig. 1 a,b). Data of 66 patients received related BMT were further analysed by both univariate and multivariate analyses. Patients transplanted at advanced stage of disease had significantly poorer clinical outcome. Only 1 of 11 group III patients remained alive at the time of present analysis. That patient developed cytogenetic relapse at 38.6 months post-BMT and successfully induced into cytogenetic remission with α interferon.

The time lapse from diagnosis to BMT did not turn out to be significant in our analysis. Besides, mild acute GvHD (grade I to II) did not seem to have any effect on their disease with a cumulative probability of relapse rate of 21.8% at 4 years. However, patients developing severe acute GvHD (grade III to IV) had uniformly poor outcomes. Similarly, there appeared towards a low probability of relapse (16.9% vs. 35.2%) in those developed

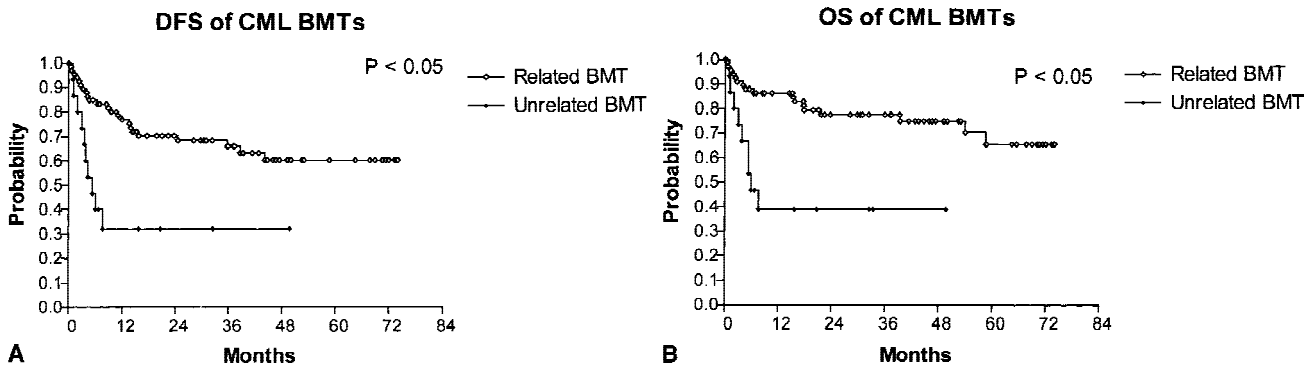

Fig. 1. (**a**) and (**b**) show the disease-free survival (DFS) and overall survival (OS) for patients with CML underwent related and unrelated BMT.

chronic GvHD, although it did not reach statistical significance.

In multivariate analysis, time from diagnosis to BMT and age were used as continuous variables, whereas both acute and chronic GvHD were used as time-dependent variables. Advanced disease came out to be an independent positive predictor for relapse with RR = 2.01 (95% CI = 1.48–2.73), whereas presence of chronic GvHD reduced the chance of relapse to 0.09 (95% CI = 0.02–0.38).

DISCUSSION

We consecutively collected data from 81 allogeneic BMT in Chinese patients with CML over the past 6 years. We found the clinical outcome after BMT was similar to those reported in the literature [6–8,12]. Both OS and DFS after related BMT in our series were more than 60% at 4 years. When these were further analysed, those remained in the first chronic phase had the best outcome. We also determined that advanced disease stage was a significant prognostic factor in both univariate and multivariate analyses that were inconsistent with that of the registry findings [13].

The high incidence of both acute and chronic GvHD in our cohort were similar to that reported in other studies [8,9]. Forty-seven and one-fourth percent of them after related BMT developed acute GvHD and 10.7% of patients had severe grade III to IV acute GvHD, which included significant morbidity and mortality. In addition, acute severe GvHD was particularly frequent in patients after unrelated BMT (46.7% vs. 11%). These were of clinical importance because serious complications were more commonly observed after unrelated BMT and their longer time to platelet independence also made management difficult. However, it remains to explore an effective mean for both prophylaxis and treatment of acute and chronic GvHD while maintaining graft-versus-leukaemia effect.

In conclusion, we found allogeneic BMT is feasible in Chinese patients with CML. The outcome is more favourable in those in their first chronic phase with HLA-identical sibling donor. However, because there is a high incidence of acute GvHD, better means of GvHD prophylaxis should be explored. We conclude that the option of BMT should always be offered to most patients early in their disease course.

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